REMARKS

Status of the Claims

Claims 1, 10-13, 15 and 23-38 are pending in the application.

Claims 1, 10-15 and 23-38 have been rejected.

Claims 1 and 15 have been amended and new claims 39-43 have been added.

Upon entry of this amendment, claims 1, 10-13, 15 and 23-43 will be pending.

Summary of Amendment

Claim 1 has been amended to remove the amendment introduced in Applicant's previous response. Support for this claim as amended will be discussed below. New claims are supported throughout the application, including for example, where the application states, "the antibody bind activating Fc-receptors with at least the same affinity as wildtype antibody" (Specification, as filed, page 6, lines 10-11); "while retaining or enhancing binding to FcRIIA and FcRIIIA" (Specification, as filed, page 7, line 17); or that the antibody has "unchanged, or even enhanced, affinity" (Specification, as filed, page 15, line 20).

Claim 15 has been amended to correct the dependency.

No new matter has been added.

Enablement

Claims 1, 10-15 and 23-38 are rejected under 35 U.S.C. §112, first paragraph, because it is asserted that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention for the same reasons set forth in the previous Office Action, mailed April 22, 2002. It is the examiner's position that the specification does not provide sufficient guidance and examples as to which modifications would be acceptable to retain these specific structural and functional properties of claimed antibodies to be used in the claimed method for enhancing cytotoxicity elicited by antibody *in vivo*, which method comprises disrupting activation of SHIP by FcRIIB. In addition, the term "modifying"

encompass any substitution, deletion or insertion (page 14, lines 13-16 of Specification as filed) of Fc portion of the antibody that will affect their structural and functional properties. The Examiner asserts that protein chemistry is probably one of the most unpredictable areas of biotechnology and that it is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. Applicant respectfully disagrees.

Initially, in the Office's previous non-Final Office Action (mailed January 28, 2004) the Office alleged that the specification requires the claim to recite that the therapeutic antibody retains or binds to FcRIIA and FcRIIIA. (Office Action, page 3, mailed January 28, 2004). Additionally, the Office alleges that

> Applicant clearly stated that to practice the invention it would be essential that antibodies, while reducing their binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, still retaining or enhancing binding to FcRIIA and FcRIIIA.

(Office Action, page 3, mailed January 28, 2004, emphasis in original). Applicant respectfully disagrees. A search of the present application, finds that the word "essential" appears only once in the application. The application states, "SHIP, an inositol polyphosphate 5-phosphatase, is essential for the biological activity of FcRIIB." (specification, as filed, page 13, lines 21-22). Nowhere in the present application does it "clearly state" what the Office alleges. The Office refers to only one section of the specification that discloses a therapeutic antibody that has reduced binding to FcRIIB while retaining or enhancing binding to FcRIIA and FcRIIIA (Specification, as filed, page 7, line 17). However, this section, is at most a more specific embodiment of the present invention. Although, the embodiment may be described as "preferred" it is only one of many embodiments of the invention. The Office is respectfully reminded that the reading of limitations into the claims from the specification is strictly prohibited.

Additionally, the specification, clearly states that the broader invention of an antibody with reduced binding to FcRIIB without the limitation that it must retain binding to FcRIIA and

FcRIIIA. For example, the abstract of the present application states, "The invention further provides an antibody...a variant Fc region that results in binding to the antibody to FcγRIIB with reduced affinity." The abstract ***does not clearly state*** "that to practice the invention it would be essential that antibodies, while reducing their binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, still retaining or enhancing binding to FcRIIA and FcRIIIA."

The "Summary of the Invention" section of the specification states "antibody binding is inhibited by modifying the Fc portion of the antibody to reduce its affinity for FcγRIIB." (specification, as filed, page 6, lines 6-7). The "Summary of the Invention" ***does not clearly state*** "that to practice the invention it would be essential that antibodies, while reducing their binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, still retaining or enhancing binding to FcRIIA and FcRIIIA." Instead, the "Summary of the Invention" only states that in some embodiments, "the antibody binds activating Fc-receptors with at least the same affinity as wildtype antibody." By stating, that something is "preferable" is not the same as "essential" as the office seems to assert.

In the "Detailed Description" the specification states that the disruption of SHIP activation can occur by disrupting the binding to FcRIIB. (Specification, page 7, lines 14-17). The description does state "In particular, by disrupting therapeutic antibody binding to the inhibitory Fc receptor FcRIIB while retaining or enhancing binding to FcRIIA and FcRIIIA," however, this is nothing more than a specific embodiment of the invention. (Specification, page 7, lines 14-17). There is nothing in this statement that clearly states, "that to practice the invention it would be essential that antibodies, while reducing their binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, still retaining or enhancing binding to FcRIIA and FcRIIIA," as the office alleges. Instead, the Office refers to a more specific embodiment of the invention that is claimed as a dependent claim of the present invention (See claims 39-43).

Furthermore, the specification states "In a preferred embodiment, antibody binding is inhibited by modifying the Fc portion of the antibody to reduce its affinity for FcγRIIB."

(Specification, as filed, page 13, lines 28-29). There is nothing in this statement that clearly states, "that to practice the invention it would be essential that antibodies, while reducing their binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, still retaining or enhancing binding to FcRIIA and FcRIIIA," as the office alleges.

As the final example, that the portion of the specification referred to the Office does not clearly state that an element is essential, the specification states

> In a specific embodiment, a modified antibody variant of the invention has reduced affinity for FcRIIB, but unchanged, or even enhanced, affinity for the stimulatory FcRs, FcRI and FcRIII.

(Specification, page 15, lines 19-21). This statement, makes clear that the feature that the Office alleges is essential is only a "specific embodiment," not an essential one.

As briefly discussed above, the Office is importing limitations into the claims. But this is not permitted. See, e.g., *Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 950, 28 USPQ2d 1936, 1938 (Fed. Cir. 1993) ("It is improper for a court to add extraneous limitations to a claim, that is limitations added wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim."

As Applicants discussed above, the Office alleges that the claims are not enabled for a variety of reasons. The Office states that "The claims as written encompass a broad genus of therapeutic antibody with an ***unlimited number*** of possibilities with regard to the modified Fc region sequence." (Final Office Action, page 2-3, mailed June 2, 2006, emphasis added). The Office action also states that the specification does not teach how to make an antibody with reduced binding for FcRIIB. Applicants respectfully disagree.

It is well established that the requirements of §112, first paragraph, are met so long as: (1) the invention is described in the specification as broadly as it is claimed; and (2) the information provided in the specification is sufficient for persons of ordinary skill in the art having the specification before them to make and use the invention. A recent Federal Circuit case regarding the enablement of an invention is quite instructive.

In Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1369-60 (Fed. Cir. 2006), the claims at issue were directed to vaccine comprising inactivated essential genes in poxvirus. The claims were challenged as not being enabled because the specification did not identify any essential genes in poxvirus or describe the inactivation of such genes, (2) vaccines based on vaccinia (a type of poxvirus) had not yet been produced, and (3) the bulk of the Inglis specification was directed not to poxviruses but to herpesviruses. (Id.). The situation is similar as to, here, where the Office alleges that the specification does not describe any working examples of the therapeutic antibodies that are used in the claim and that "the absence of the structure" is indicative that the claimed invention is not enabled (Office Action, page 3).

The Board of Patent Appeals and Interference, which was affirmed by the CAFC, found that the claims were enabled even with the alleged deficiencies. The Board supported its conclusions by stating the specification contained "extensive disclosure of the selection of an essential gene, its deletion or inactivation and the production of a mutated virus with said deleted or inactivated gene" *Id.* at 1635. The Board also noted "the mere fact that the experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered to be 'undue' in this art. Indeed, great expenditures of time and effort were ordinary in the field of vaccine preparation." *Id.* Accordingly, the Board held that the claims were enabled. *Id.*

The CAFC further explained, the evidence demonstrated the sequence of the virus was known and that the essential regions were also known to one of skill in the art. *Id.* The court explained that such disclosure is not needed in the application when it is readily available to one of ordinary skill in the art. *Id.* A "patent need not teach, and preferably omits, what is well known in the art." *Id.* (citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed.Cir.1987).

The present application clearly teaches and enables one of skill in the art to make an antibody that has reduced binding to the FcRIIB receptor. For examples, the specification states, "A number of references describe techniques for modifying Fc portions to modulate binding

affinity for FcRs." (Specification, as filed, page, line 29 to page 14, line 3). The sequence of the Fc Region was known and can easily be modified by any mutagensis technique known to one of skill in the art. Furthermore, a reference published after the priority date of the present application indicates nothing more than routine experimentation is needed to make an antibody with reduced binding to FcRIIB. In the accompanying declaration, Dr. Ravetch states that the Shields reference (JBC, Vol. 276, pp. 6591-6604 (2001), attached hereto) made antibodies that have reduced binding to FcRIIB. For example, Table I (see, page 6595) lists a number of Fc variants that have reduced binding to FcRIIB. To create the mutants, the authors in Shields only used site-directed mutagenesis (see, Declaration, ¶ 3, and Shield Reference, page 6592, top of right column). This type of mutagenesis is nothing more than routine experimentation that anyone of ordinary skill in the art can do without any undue burden. The assays used were also nothing more than routine. If the Office maintains that such methods are not routine Applicant respectfully requests for sufficient reasons as to why the methods used in the Shields reference are more than routine experimentation.

The absence of working examples is not also not enough evidence that the present application is not enabled. Like in *Falkner*, which also did not have working examples, there is sufficient disclosure how to make and use the antibodies in the claimed invention. The Office alleges that the art is unpredictable and refers to the Pearse reference (Immunity, Vol. 10, 753-760, (1999)). Specifically, the Office refers to page 756 that the Office alleges that "interpretation of data obtained on mice deficient in FcγRIIB is complicated, since animals deficient in the inhibitory receptors have different responses compare[d] to control ones." (Office Action, page 3). Applicants respectfully asserts that the Office is mischaracterizing the Pearse reference and is, therefore, the use of the Pearse reference is misplaced.

The Pearse reference states,

> The B cell expresses only the inhibitory Fc receptor FcγRIIB without a corresponding activation FcR. However, coligation of FcγRIIB and an activation counterpart, the BCR, does occur during interaction with ICs, when antigen binds to the BCR and the Fc

> domains interact with FcγRIIB. This coengagement suggests a mechanism whereby ICs function as feedback regulators of B cell activation. In vitro, ICs are potent inhibitors of B cell activation stimulated through the BCR. However, in vivo, mice deficient in FcγRIIB have modestly elevated serum antibody titers to both thymic-dependent and thymic-independent antigens. ***Interpretation of those results is complicated*** by the fact that the primary site for the interaction of B cells with ICs is in the germinal center, where ICs are retained by follicular dendritic cells (FDCs).

(Pearse Reference, page 756, right column, 2nd ¶, emphasis added). This section of the reference clearly does not state that interpretation of ***any*** data obtained using mice deficient in FcγRIIB. Instead, the sentence referred to by the Office is only stating that the results specifically referred to are complicated and not answered completely. The Pearse reference, does not state that the claimed invention is unpredictable.

Furthermore, the claims provide structure to the claims and are not based solely on function as the Office has alleged. Claim 1 recites that the therapeutic antibody whose cytotoxicity is enhanced by the present invention retains or has enhanced binding to activating Fc receptors and that the Fc region of the antibody ***is at least 80% homologous*** with a native Fc region. As discussed above, the sequence or region comprising a native Fc region is known and is not required to be re-taught by the present application. A "patent need not teach, and preferably omits, what is well known in the art." *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed.Cir.1987). Claims 23 and 24 further limit the percent homology to 90 and 95% respectively. Claims 25-29 further limit the claims with respect to amino acid substitutions. Claims 30-34 further limit the claims with respect to amino acid additions. Claim 33 and 34 further limit the claims with respect to amino acid deletions.

The claims variously recite limitations on the structural changes made to the therapeutic antibody and specific functions which the final product possesses. One skilled in the art could produce molecules according to the invention without undue experimentation as evidence by the

teachings of the specification, the declaration, and the Shields reference, which demonstrates that such antibodies can be made and used without undue experimentation.

The claims also do not encompass an "unlimited number" of possibilities as the Office alleges. The claims are restricted to antibodies that have reduced binding to FcRIIB and also have at least 80% homology to a native Fc region. Although the number of mutations that can be made may be large, it is certainly a finite number and not unlimited. However, the number of possibilities that can be created is not relevant to enablement. In *In re Wands*, 8 USPQ2d 1400, 1405 (Fed. Cir. 1988), a large number of hybridomas were made (143) and only 4 actually fell within the scope of the claim. That is equal to only 4 percent, which the court found was sufficient for enablement because the although the type of experimentation may have been time consuming and numerous, it was not undue because it was nothing more than routine experimentation to create the hybridomas. Here, although the many antibodies may be made and tested to determine if they have reduced binding to FcγRIIB, the methods are all routine, just like in *In re Wands*. Accordingly, the present invention is enabled.

The claims are in compliance with the enablement requirement of the first paragraph of section 112. Applicant respectfully requests that the rejection of claims 1, 10-15 and 23-38 under 35 U.S.C. §112, first paragraph, because it is asserted that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, be withdrawn.

Written Description

Claims 1, 10-13 and 23-38 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed. The Office alleges that

> There does not appear to be an adequate written description in the specification as-filed how to ***make*** an antibody that have a reduced

> binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, while retaining or enhancing binding to FcRIIA and FcRIIIA and use them in a method for enhancing cytotoxicity elicity by antibody *in vivo*, which method comprises disrupting activation of SH2 domain containing inositol 5-phosphatase (SHIP) by FcRIIB.

(Office Action, page 5, emphasis added). Applicant respectfully disagrees.

Although this is a written description rejection the Office appears to be once again making an enablement rejection, which has already been made (see above). By stating, that the specification does not state "how to make" the antibody that is described in the specification, the Office is admitting that the antibody is described and is more or less repeating the enablement rejection. The Office further alleges that the specification

> At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work.

(Office Action, page 5). However, this is not the case here. The claim clearly states that one uses an antibody that comprises an Fc region that is at least 80% homologous with a native Fc region that has reduced binding to FcγRIIB. This is not an "attempt to preempt the future before it has arrived" as the Office alleges, but rather the specification gives a detailed description of what structure the antibody should have. One of skill in the art would clearly understand that the specification, as-filed, describes the claimed invention.

The case law cited by the Office in support of this rejection is not relevant to the pending claims in the present application. The cases cited by the Office are directed, *inter alia*, to written description defects in claims directed to nucleic acid sequences of genes that had not been cloned. This fact pattern does not apply to the present invention. Instead, as discussed below, more current case law is applicable to the present invention, which supports Applicants' position that the claims satisfy the written description requirement.

The present invention is not dissimilar to *Capon v. Eshhar* where the Federal Circuit overturned the Board of Patent Appeals and Interferences ("Board") rejection of claims for lack

of written description. See *Capon v. Eshhar*, 418 F.3d 1349, 1359-1360, (Fed. Cir. 2005). In *Capon,* the claims recited chimeric DNAs (or genes) comprising DNA encoding , for example, a single chain Fv domain of a specific antibody and the transmembrane and cytoplasmic domain of an endogenous protein. *Id. at* 1352-1353. The Board had rejected such claims for lack of written description, arguing that genetic material was being described in terms of the functional characteristics of the protein encoded. *Id.* at 1354-1355. The Board, relying upon much of the same precedent relied upon by the Office in rejecting Applicants' claims, was requiring complete disclosure of the embodiments. *Id.*

In response, the parties argued, *inter alia*, that the chimeric genes are produced by selecting and combining known DNA segments, using known procedures. *Id.*, at 1355. Notably, the Board did not dispute that persons in the field could determine the structure or formula from the known structure or formula of the components. *Id.* The Federal Circuit observed that none of the cases relied upon by the Board required a re-description of what was already known. *Id.*, at 1357-1358. The court stated,

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. . . .When the prior art includes the [allegedly lacking] information, precedent does not set a per se rule that the information must be determined afresh.

Id., 1358. In the present case, as in *Capon*, the components are known. The sequence of the Fc region is known and the methods to modify the Fc region of antibody are also known. Notably, the Office has not argued to the contrary.

Capon was recently cited approvingly in another Federal Circuit decision regarding written description. In *Falkner v. Inglis*, 448 F.3d 1357, (Fed. Cir. 2006, also discussed above), the losing party in the interference argued that the claims did not satisfy the written description requirement because the Application did not provide the full description (*e.g.* sequences) of the essential genes of the Poxvirus, had not produce a vaccine based without the essential genes of the poxvirus, and that the specification was directed not to poxvirus but to a different type of

virus. *Id.*. Notably, the Board properly rejected these arguments, finding writing descriptive support. The Federal Circuit agreed and held that

> [I]n accordance with our prior case law, that (1) examples are not necessary to support the adequacy of a written description (2) the written description requirement may be met...even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

Id. at 1366.

The present application satisfies the written description requirement of 35 U.S.C § 112 because provides a sufficient description of the antibody, which includes a structural limitation that it be at least 80% homologous to the native Fc region. The *Falkner* decision reinforces and emphasizes that there is no rule that the application must contain a recitation of every identifying characteristic of every biological macromolecule when the molecules are known to one of skill in the art.

Accordingly, a requirement to describe the sequence of the modified antibody is not necessary because the sequences of the Fc regions of a particular antibody are known and thus requiring Applicant to re-teach every sequence is "unnecessary" and in not in agreement with the Federal Circuit's decisions in *Falkner* and *Capon*.

In explaining that there is no *per se* rule to describe what is already known, such as the sequences of the Fc region, *Falkner* quoted *Capon*, where the court stated

> The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

Falkner at 1367, *Capon* at 1357. Here, the state of the art at the time the present application was filed was such that one of skill in the art would understand what is meant by a therapeutic antibody with an Fc region that is at least 80% homologous to a native Fc region and has reduced binding to FcγRIIB. And, information regarding antibodies and how to modify antibodies is easily accessible in the literature and is also described in the present application.

However, the present application provides written description support of the claim that falls within the scope of the claims in such a way that one of ordinary skill in the art would understand that Applicants were in possession of the invention at the time the application was filed. For example, in the Summary of the Invention (specification, as-filed, page 6) describes the claimed invention. The specification, also describes an antibody with reduced binding to FcγRIIB. Additionally, throughout the specification, the application describes antibodies and uses for them. For example, Example 2, beginning on page 36 of the specification, describes the generation of an antibody with reduced binding to FcγRIIB. Although, Example 2, is prophetic, it clearly demonstrates that Applicant was in possession of the invention at the time the application was filed. As the Federal Circuit has recently reemphasized, working examples are not required for the written description requirement. *Falkner* at 1366.

Furthermore, in the present application, the structure as claimed is clear, the function is clear and the correlation between the two is clear. Claim 1 refers to an Fc region that is 80% homologous to a native Fc region. Claim 23 refers to an Fc region that is 90% homologous to a native Fc region. Claim 24 refers to an Fc region that is 95% homologous to a native Fc region. The structure of these molecules are clearly defined. Claims 25-38 refer to Fc regions that are 80% homologous to a native Fc region and have limitations with respect to substitutions, additions or deletions. The structures are known as are the functions which are associated with Fc region including binding to the Fc receptors.

The claims are in compliance with the written description requirement of the first paragraph of section 112. Applicant respectfully requests that the rejection of claims 1, 10-13 and 23-38 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not

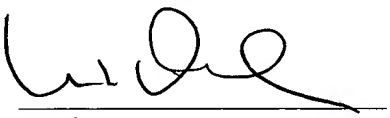
described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention be withdrawn.

Conclusion

In view of the foregoing, Applicant submits that the claims 1, 10-13, 15 and 23-43 are in condition for allowance. An early indication of allowability and notice of allowance is earnestly solicited. Applicant invites the Examiner to contact the undersigned at 215.665.5592 to clarify any unresolved issues raised by this response.

As indicated on the transmittal accompanying this response, the Commissioner is hereby authorized to charge any debit or credit any overpayment to Deposit Account No. 50-1275.

Respectfully submitted,



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Date: Dec 4 2006

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Attachments:
1. Declaration by Dr. Jeffrey V. Ravetch
2. Shields Reference, J. Biol. Chem., Vol. 276, Issue 9, 6591-6604, March 2, 2001.